Acute and chronic effects of anteromedial globus pallidus stimulation in Parkinson’s disease

Franck Durif, Jean-Jacques Lemaire, Bérengère Debilly, Gérard Dordain

Abstract

Objective—To evaluate the effects of acute and chronic stimulation in the anteromedial part of the globus pallidus internus (GPI) on the symptoms of patients with Parkinson’s disease.

Methods—Six patients with severe Parkinson’s disease (Hoehn and Yahr stage 4–5 in “off” drug condition) with motor fluctuations and levodopa induced dyskinesia (LID) were operated on. Chronic electrodes were implanted in the anteromedial GPI bilaterally in five patients and unilaterally in one patient. The effect of stimulation via the four contacts for each electrode (n=11) was assessed postoperatively on the contralateral parkinsonian signs in the off condition and on the contralateral and ipsilateral LID in the “on” condition. The core assessment program for intracerebral transplantation protocol was performed before surgery and then 1, 3, and 6 months after surgery in on and off condition and in on and off stimulation conditions.

Results—Stimulation performed postoperatively showed a significant improvement (p<0.05) by 47% (contralateral rigidity) and 32% (contralateral bradykinesia) when stimulation was applied through the distal contact. Levodopa induced dyskinesias were improved by 95% (contralateral LID) and by 66% (ipsilateral LID) when stimulation was applied through the distal contact. Six months after the surgery, GPI stimulation in the off condition led to a mean improvement in the motor score of UPDRS by 36%. The mean daily duration in the off state decreased by 52% (p<0.05). The mean duration of LIDs decreased by 68% (p<0.05) and their severity by 53% (p<0.05).

Conclusion—Chronic stimulation in the anteromedial GPI shows that this is a safe and effective treatment for advanced Parkinson’s disease with benefit sustained for at least 6 months.

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Keywords: Parkinson’s disease, chronic stimulation, globus pallidus

Motor complications, such as levodopa induced dyskinesias (LIDs) and motor fluctuations, commonly occur in patients with Parkinson’s disease chronically treated with levodopa. Changing the treatment such as spreading out levodopa doses throughout the day, using sustained release levodopa, and adding dopamine agonists usually temporarily improves motor complications, which can reappear and worsen when the disease progresses.

Surgical treatment may be proposed to patients not satisfactorily improved by medical treatment. Recently, there has been a resurgence of interest in pallidotomy for the treatment of advanced Parkinson’s disease. This surgical procedure dramatically reduces contralateral LIDs but also improves all cardinal parkinsonian signs such as rest tremor, rigidity, bradykinesia, and gait dysfunction. Equivalent results have recently been shown with chronic high frequency deep brain stimulation, which is an alternative surgical non-lesional treatment for Parkinson’s disease.

Currently, the optimal lesion site of pallidotomy or pallidal stimulation remains uncertain. In the early 1950s neurosurgeons investigated lesion of the anterodorsal region in the internal portion of the globus pallidus (Gpi). In 1960, Svennilson et al reported that stereotactic lesions in the ventroposterolateral pallidum markedly improved the clinical results. Since the recent surgical reassessment of pallidotomy by Laitinen et al neurosurgeons have performed pallidotomy or high frequency deep brain stimulation in the ventroposterior GPI. However, a recent report has shown a dramatic improvement of cardinal parkinsonian signs in a patient after bilateral chronic anterior pallidal stimulation.

In an attempt to confirm the results of this pilot study and thus to re-evaluate the anterior target in Gpi, we assessed the motor effects of acute electrical stimulation on different parts of the anterior Gpi on parkinsonian signs and on LID in patients after implantation of quadripolar electrodes. We also evaluated the effects of chronic anterior pallidal stimulation in patients after a 6 month period.

Methods

Patients
Six patients (four men, two women) fulfilling the requirements for the United Kingdom Parkinson’s Disease Society Brain Bank of mean age (SEM) 64 (3) years were included after acceptance of the study by the ethics committee of Auvergne University (table 1). These patients gave written consent to their participation in this study. The mean duration of the disease was 15 (2) years and the mean duration of the treatment was 12 (2) years. Before surgery, the levodopa daily dose (plus peripheral decarboxylase inhibitor) was 1200 (260) mg. Four of the patients received a dopamine

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Table 1  Patient’s characteristics at baseline

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Disease duration (y)</th>
<th>Dosage of levodopa (mg/day)</th>
<th>Motor part of UPDRS</th>
<th>Hoehn and Yahr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>F</td>
<td>13</td>
<td>1000</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>F</td>
<td>10</td>
<td>1050</td>
<td>41</td>
<td>6.5</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>F</td>
<td>20</td>
<td>800</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>M</td>
<td>15</td>
<td>1050</td>
<td>30</td>
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<tr>
<td>5</td>
<td>51</td>
<td>M</td>
<td>10</td>
<td>2500</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>M</td>
<td>25</td>
<td>900</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Mean</td>
<td>64 (3)</td>
<td>15 (2)</td>
<td>1200 (260)</td>
<td>36 (2)</td>
<td>9 (1)</td>
<td>4.3 (0.2)</td>
</tr>
</tbody>
</table>

Values in parentheses are SEM.

agonist, one patient received tolcapone, and two patients received subcutaneous injections of apomorphine. Despite optimisation of antiparkinsonian treatment, severe motor fluctuations and monophasic and dysphasic levodopa induced dyskinesias still persisted in all of the patients.

Their mean baseline unified Parkinson’s disease rating scale (UPDRS) (parts I+II+III) was 60 (6). All patients had an excellent response to levodopa (mean improvement 72 (33)% (table 1)). The mean duration of LIDs was 2.5 (1.0) hours and their severity was 3.0 (0.6) (items 32–33 from part IV of the UPDRS). The mean duration of daily time spent in the “off state was 1.6 (0.8) hours (item 39 from part IV of the UPDRS). All patients had no depression (mean mental status of Folstein 28 (1). Presurgical MRI performed in the 3 months before surgery was normal.

NEUROSURGICAL PROCEDURE

A week before surgery, an MRI obtained in stereotactic conditions (sMRI) using a stereotactic frame (Leksell model G, Elekta Instruments, Stockholm, Sweden) with a repositioning system (Elekta Instruments, Stockholm, Sweden) was carried out. An iodoventriculography was also performed on the first five patients. The sMRI (Siemens Magnetom 1 Tesla, matrix 256×256) consisted of three sequences of orthogonal plans with contiguous slices 3 mm thick. T2 weighted images (TR=2500 ms, TE=20 ms) were achieved in a frontal and an axial plane and T1 weighted images (TR=450 ms, TE=15 ms) in a sagittal plane. Images were then transferred to a workstation. We used a stereotactic software package (Brainscan, Brainlab, Germany) to locate the brain structures in sMRI spaces. The target of the GPi was the vertex of the nucleus facing the knee of the internal capsule. The software calculated the coordinates of the target and the simulated electrode trajectory. A week later, the stereotactic frame was repositioned. A semimicroelectrode (FHC, Brunswick, USA) was advanced along the selected trajectory given by the software and stimulation (130 Hz, pulse width 60 µs, 0–10 mA) was performed millimeter by millimeter starting 10 mm above the target. Clinical and side effects of the stimulation were evaluated by a neurologist (FD) unaware of the stimulation condition. We used tremor, rigidity (wrist, elbow, ankle), and bradykinesia (pronosupination of the hand, thumb-index tapping) subjective assessments (improvement or aggravation percentage from the prestimulation status) to evaluate the clinical effect of stimulation. The site chosen for the definitive electrode placement was determined during stimulation by the maximum improvement of contralateral upper and lower limb tremor and rigidity, and upper limb bradykinesia. A chronic deepbrain stimulation quadripolar electrode (3387, Medtronic, Minneapolis, MN) was implanted to replace the semi-microelectrode directed toward the target. The electrode had four contacts 1.5 mm long with a distance of 1.5 mm and with an external diameter of 1.3 mm. Stereotactic x ray film controls were performed during the procedure to verify that there was no electrode shift. One electrode on each side was implanted during the same procedure for five patients. All patients had a postoperative MRI a week after the surgical procedure before the implantation of the programmable stimulator (Itrel II, Medtronic) in the subclavicular area.

PATIENT ASSESSMENTS

Clinical effect of postoperative acute stimulation

The effect of electrical stimulation via the four contacts of the electrode was assessed on the parkinsonian signs and on LIDs within the 12 days after the surgical procedure. Parkinsonian signs were assessed in the off condition after interruption of the antiparkinsonian treatment for at least 12 hours using items from the UPDRS part III: contralateral limb rigidity, contralateral bradykinesia (thumb-index tapping), and contralateral upper and lower limb rest tremor. The clinical effect of electrical stimulation for each electrode (six patients, 11 electrodes) was evaluated by using improvement or aggravation percentage from clinical evaluations performed without stimulation. The LIDs were evaluated in the “on” state during two acute suprathreshold levodopa challenges on 2 consecutive days using a subjective scale (0=no abnormal movement; 4=movement resulting in severe disability) on the four limbs, on the trunk, the neck and face (maximum score 28), during rest and after an activation task (speaking aloud). The stimulation mode was unipolar with a negative electrode contact. The pulse width and the frequency of the stimulation current were respectively kept at 130 Hz and 60 µs. The voltage amplitude was progressively increased from 0 to 5 V. Clinical evaluation was performed at each voltage step. Before each assessment, a stimulation period of at least 3 minutes (parkinsonian symptoms) or at least 15 minutes (evaluation of LIDs) was used. A 10 minute period without stimulation was allowed before evaluation of another contact, showing that the clinical indices studied returned to the baseline.

Clinical effect of chronic stimulation

Patients were evaluated according to the core assessment program for intracerebral transplantation (CAPIT) protocol. The evaluations, which were videotaped, were rated during the off state and during the best on state, as agreed by the patient and physician. The clinical evaluation was performed before
surgery and then on the 1st, 3rd, and 6th month in on-off drug conditions and on-off stimulation conditions. Furthermore, patients kept diaries for at least 3 days before each clinical assessment in which they noted the diurnal time spent with good motor function (on state), poor motor function (off state), and motor function accompanied by incapacitating involuntary movements (on state with dyskinesias). Chronic stimulation was adapted from the results that were obtained during the acute assessment period with a view to reducing the duration and the severity of LIDs, and the time spent in the off state. For each patient, stimulation indices (amplitude voltage, pulse width, frequency) were adapted every day for 2 weeks and then every month for a period of 3 months in relation with their motor status.

LOCATION OF THE ELECTRODE CONTACTS
Coordinates of the contacts which gave the best clinical results during the peroperative assessment (distal contact) and 6 months after the surgical procedure were determined from the control radiograph performed at the end of the surgical procedure. The coordinates of all contacts for the six patients were automatically placed within the pallidum, which was reconstructed for each patient in three dimensions from frontal and horizontal preoperative sMRI slices with stereotactic software (fig 1). The distances between the centre of each contact and the medial, dorsal, and ventral boundaries of the pallidum were measured for all patients (bilaterally for five patients). Furthermore, for the first five patients in which a ventriculography was performed, we also calculated the location of the distal contacts and the contacts which gave the best clinical results 6 months after the surgical procedure with reference to the ventriculographic landmarks of Talairach et al2: the laterality from the median sagittal plane of the third ventricle, the anterior position from the midpoint of the intercommissural line (Mic), and the vertical position in relation to the intercommissural line (Icl) (above or below).

STATISTICAL ANALYSIS
Values were expressed as mean (SEM). Rest tremor was not analysed because only one patient had a stable tremor in the off state. Contralateral and ipsilateral dyskinesias were calculated from the sum of the lower and upper limbs, which were items from the dyskinesia scale. The effect of the voltage amplitude for each contact electrode and for each electrode on contralateral parkinsonian signs (rigidity and bradykinesia), and on contralateral and ipsilateral LIDs, was analysed using analyses of variance (ANOVA) with repeated measures in which the repetition factor was the voltage amplitude from 0 to 5 V. When the ANOVA showed a significant difference, the Newman-Keuls test was performed. According to the distribution of data, a Wilcoxon signed rank test and a paired Student’s t test were used to compare assessment performed before surgery and 6 months afterwards. Significance was declared at p \leq 0.05

Results

LOCATION OF THE ELECTRODE CONTACTS

Location in relation to the boundaries of the pallidum

The mean distances (mean of both sides) from the distal active contacts to the boundaries of the pallidum were respectively to the medial
Effect of acute postoperative stimulation on contralateral dyskinesia assessed during an activation task (speaking aloud) for each contact of electrodes (n=11). The effect of amplitude voltage on every contact was analysed by ANOVA with repeated measures. 

Figure 4

Figure 5

boundary of the pallidum 2.4 (0.7) mm, to the dorsal boundary 4.2 (0.5) mm, and to the ventral boundary 0.4 (0.4) mm. The mean distance from the active contacts 6 months after the surgery (contact 1 bilaterally in three patients; contacts 2 bilaterally (apart for one patient with unilateral stimulation) in three patients) to the boundaries of the pallidum were respectively to the medial boundary 2.5 (0.6) mm, to the dorsal boundary 2.5 (0.5) mm, and to the ventral boundary 4.2 (0.4) mm. The mean distances from the proximal contact 3 were respectively to the medial boundary of the pallidum −0.8 (1.5) mm (medial to the medial boundary), to the dorsal boundary −0.1 (0.6) mm (above the dorsal boundary), and to the ventral boundary 8.1 (0.6) mm.

Location in relation to stereotactic landmarks
For the distal contacts, the mean laterality was 15.3 (0.4) mm, the mean anterior position was 9.3 (0.6) mm in front of the Mic, and the vertical position was 0.8 (0.9) mm above the Icl. For the active contacts 6 months after the surgery, the mean laterality was 15.4 (0.4) mm, the mean anterior position was 11.5 (0.6) mm in front of the Mic, and the vertical position was 2.1 (0.3) mm above the Icl.

Effect of postoperative acute stimulation
Parkinsonian signs (rigidity and bradykinesia)
Analyses of variance showed a significant improvement of rigidity when stimulation was applied through the four contacts: contact 0 (distal contact), \( F(8)=11.6, p<0.0001 \); contact 1, \( F(8)=9.8, p<0.0001 \); contact 2, \( F(8)=8.4, p<0.0001 \); contact 3 (proximal contact), \( F(8)=5.6, p<0.0001 \). Newman-Keuls tests showed a significant improvement (\( p<0.05 \)) of rigidity: (1) at 3 V, 4 V, and 5 V amplitude compared with rigidity evaluated without stimulation when electrical stimulation was applied through contacts 0, 1, and 2; (2) at 5 V amplitude when stimulation was applied through contact 3. For each contact, rigidity improved progressively with the voltage and reached a plateau at 3 or 4 V. The maximum percentage improvement decreased when stimulation was applied from contact 0 to contact 3: at optimal amplitude voltage, the rigidity percentage improvement was 47% (contact 0), 38% (contact 1), 30% (contact 2), and 20% (contact 3) (fig 2).

Analyses of variance also showed significant improvement of bradykinesia only at contact 0 (\( F(8)=3.7, p=0.007 \)) and contact 2 (\( F(8)=3.4, p=0.01 \)). Newman-Keuls tests showed a significant improvement (\( p<0.05 \)): (1) At 3 V, 4 V, and 5 V amplitude compared with bradykinesia evaluated without stimulation when electrical stimulation was applied on the contact 0; (2) at 5 V amplitude when stimulation was applied on contact 2. At optimal amplitude voltage, the maximum improvement found was 32% (contact 0), 22% (not significant) (contact 1), and 26% (contact 2). No clinical effect was detectable when stimulation was applied through contact 3 (fig 3). An aggravation of contralateral bradykinesia by 30% was found when stimulation was applied through the four contacts with amplitude voltage higher than 3 V for two of the electrodes tested.

In one patient, stimulation on contacts 0, 1, and 2 led to a disappearance of contralateral off-foot dystonia which reappeared when stimulation was stopped.

Levodopa induced dyskinesias
Analyses of variance showed a significant improvement of contralateral LIDs when stimulation was at contact 0 (\( F(6)=11.1, p<0.0001 \)) and contact 1 (\( F(6)=4.15, p=0.004 \)). Newman-Keuls tests showed a significant improvement (\( p<0.05 \)) of contralateral LIDs at 4 V and 5 V amplitude compared with contralateral LIDs evaluated without stimulation on contacts 0 and 1. There was also a significant improvement (\( p<0.05 \)) of contralateral LIDs at 4 V and 5 V amplitude compared with 1 V, 2 V and 3 V amplitude when stimulation was on contact 0.

For all of the patients, when stimulation was applied through distal contact 0, contralateral LIDs progressively disappeared when the amplitude voltage increased with a maximum improvement of 95% at 4 V. In three patients (five electrodes), the parkinsonian signs progressively appeared and worsened when the amplitude voltage was higher than 4 V. On contact 1, the maximum improvement of LIDs was 66% at 5 V, without any worsening of parkinsonian signs. The LIDs reappeared with latency within 0 to 10 minutes when stimulation was stopped on the two lower contacts (0 and 1). No clear clinical effect was seen when stimulation was applied on contacts 2 and 3, from 0 to 5 V (fig 4).


**Table 1** Motor fluctuations at baseline and follow up 6 months after surgery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline</th>
<th>Follow up</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36 (2)</td>
<td>29 (4)</td>
<td>0.27</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>18.5</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
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</tr>
<tr>
<td>5</td>
<td>12</td>
<td>7</td>
<td>0.18</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>5</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Values in parentheses are SEM. p Values were calculated at baseline.

**Table 2** Stimulation indices 6 months after the surgical procedure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right pallidum</th>
<th>Left pallidum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contact</td>
<td>Amplitude (V)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
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<td>2.3</td>
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<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Figure 6: Effect of stimulation on motor part of UPDRS 3 and 6 months after surgical procedure (med=medication, stim=stimulation).

Ipsilateral LIDs were also improved when stimulation was applied on contact 0 as shown by ANOVAs (F(6)=4.7, p=0.002). Newman-Keuls tests showed a significant improvement (p<0.05) of ipsilateral LIDs at 4 V and 5 V amplitude compared with ipsilateral LID evaluated without stimulation, and at 1 V and 2 V amplitude. No significant effect was shown when stimulation was applied on contacts 1, 2, and 3 (fig 5).

**Table 3** Motor evaluations at baseline and follow up 6 months after surgery

<table>
<thead>
<tr>
<th>Medication off</th>
<th>Medication on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up</td>
<td>Follow up</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Patient</td>
<td>Stimulation</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
</tr>
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<td>3</td>
<td>42</td>
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<td>4</td>
<td>30</td>
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<td>5</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
</tr>
</tbody>
</table>

Mean 36 (2) 29 (4) p=0.07 10 (1) 7 (1) p=0.18 9 (1) 6 (1) p=0.01 5 (1) p=0.13

p Values were calculated at evaluation baseline. Values in parentheses are SEM.

**Table 4** Motor fluctuations at baseline and 6 months after surgery

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Follow up</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of dyskinesias*</td>
<td>2.5 (0.5)</td>
<td>1.0 (0.5)</td>
</tr>
<tr>
<td>Severity of dyskinesias*</td>
<td>3.0 (0.3)</td>
<td>1.5 (0.5)</td>
</tr>
<tr>
<td>Duration of &quot;off&quot; period*</td>
<td>1.7 (0.6)</td>
<td>0.8 (0.2)</td>
</tr>
<tr>
<td>Duration of dyskinesias† (hours)</td>
<td>5.2 (0.9)</td>
<td>3.0 (0.9)</td>
</tr>
<tr>
<td>Duration of &quot;best on&quot;† (hours)</td>
<td>8.6 (0.5)</td>
<td>11.8 (0.9)</td>
</tr>
<tr>
<td>Duration of &quot;off&quot; period† (hours)</td>
<td>6.5 (0.6)</td>
<td>2.8 (0.7)</td>
</tr>
</tbody>
</table>

Values for baseline and follow up are means (SEM).

*From items of UPDRS part IV.
†Calculated from diaries.
Discussion

EFFECT OF POSTOPERATIVE ACUTE STIMULATION

In this study, postoperative acute electrical stimulation in the anterior GPi induced a marked improvement of cardinal parkinsonian signs (akinesia and rigidity) when patients were in the off state, and led to a dramatic decrease in severity of contralateral and ipsilateral LIDs when patients were evaluated in the on state. At a higher voltage, blockage of the levodopa effect leading to reappearance of parkinsonian signs was found in three patients, as already reported by Krack et al. The effect of stimulation on rigidity, bradykinesia, and on LIDs predominated when stimulation was applied on the ventral contacts, and then progressively decreased when stimulation was applied on the dorsal contacts. These results are at variance from those of Bejjani et al who reported that acute stimulation in the posteroventral GPi, using the same electrode as in our study, had a striking, different effect on parkinsonism and dyskinesia when applied to two different targets of the GPi. The stimulation on the dorsal part of the Gpi led to an improvement of parkinsonian signs when patients were in the off state whereas stimulation applied on the ventral part of the GPi led to a worsening bradykinesia when patients were in the off state, but suppressed LIDs when patients were in the on state. Krack et al also reported that stimulation on the ventral part of GPi induced an improvement of rigidity whereas stimulation on the dorsal part led to a moderate improvement of akinesia.

Our different results could be explained by the fact that we have implanted electrodes more anteriorly and medially in the GPi. The volume of neural tissue affected by stimulation is probably in the order of mm³. Thus, the effect of stimulation probably predominates in the anteromedial part of the GPi although the diffusion of current can also slightly influence the posteroventral part. In our study, the distal contacts were on average 6 mm in front of, 6 mm above, and 5 mm medial to the target of Laitinen et al, and thus corresponds to the classic anterior target for pallidotomy. Furthermore, according to the stereotactic coordinates of Talairach et al, the active contacts projected into the internal part of the GPi, and into the ansa lenticularis. Moreover, the superimposition of active contacts within the pallidum showed that the electrodes are placed in the anteromedial part of the pallidum. According to the coordinates from the contacts to the boundaries of the pallidum on one hand, and the size of the GPi on the other, it may be assumed that the distal contacts were on the ventral boundary of the GPi and the contacts 1 and 2 were within the GPi (fig 1). The fact that stimulation on the proximal contact 3 does not induce any significant change of bradykinesia and LIDs relates to their anatomical location, situated above the Gpi in the anterior part of the internal capsule.

The anteromedial part of the GPi, which corresponds to the ventral pallidum, is crossed by a greater number of fibres at the origin of the outflow pathways, given the convergence of the anatomical structure to GPi output. These pathways (ansa lenticularis, lenticular fasciculus) are mainly localised above the optic tract and medially to the pallidum and project to the thalamus throughout the internal capsule. Thus, stimulation on the distal contact probably influenced the ansa lenticularis, which was localised on the ventral surface of the pallidum.

Although the effect of electrical stimulation is largely unknown, it is assumed that stimulation induced a direct or indirect neuronal inactivation, as shown by electrophysiological studies in rats. The improvement of parkinsonian signs by stimulation on the distal contact when patients were in the off state may be explained by inhibition of the Gpi, which is hyperactive after the striatal dopamine depletion seen in Parkinson's disease. The decrease of Gpi activity disinhibits the pallidal relay nuclei of the thalamus, which leads to a disinhibition of thalamocortical neurons resulting in an improvement of parkinsonian signs. Such results have been shown in PET studies in parkinsonian monkeys and in parkinsonian patients in which pallidal stimulation and pallidotomy restore the regional cerebral blood flow in the frontal cortex. Otherwise, the improvement of LIDs by stimulation on the distal contact is hard to explain by the classic model of the basal ganglia because LIDs may be considered to be linked to Gpi hypoactivity. However, a recent electrophysiological study performed on parkinsonian monkeys with dyskinesias suggests that dyskinesias could also result from an imbalance of neuronal activity within the Gpi, where hypoactive neurons were surrounded by hyperactive or unresponsive neurons. Thus stimulation of the medial Gpi could re-establish a normal balance of activity between the different neuronal networks in the Gpi leading to an improvement of LIDs.

EFFECT OF CHRONIC STIMULATION

In our study, chronic stimulation in the anterior GPi led to an improvement of parkinsonian signs and LIDs. Furthermore, stimulation significantly increases the daily duration of the on state and reduces the time spent with severe dyskinesias in this state. Moreover, stimulation significantly reduces the time spent in the off state. The fact that our chronic results are close to those reported in other studies in which stimulation was in the posteroventral portion of the Gpi, suggests that the anterior target could be as effective as the posteroventral part of the Gpi in advanced Parkinson's disease. Compared with the ventrolateral Gpi, one of the advantages of the anterior target is that it is easily located by using stereotactic MRI.

Compared with the clinical effect found during the acute assessment, the best results of chronic stimulation occurred when stimulation was applied on more proximal contacts, which were more dorsal than the distal contacts. One of the possible explanations could be that chronic stimulation on the distal contacts when patients are in the on state decreases...
LID but also induces a blockade effect of levo-
dopa at a lower voltage than during the acute
evaluation, requiring stimulation to be moved
to the proximal contacts. These results could
indicate that the stimulation condition (acute v
chronic) leads to different changes in the
activity of GPI or alternatively induces toler-
ance phenomena.

In our study, there was no permanent
morbidity associated with the surgical proce-
dure. The side effects were in relation to the
stimulation condition and always reversible by
the reduction of the amplitude voltage. Such
results have been reported in other studies
showing that the procedure of chronic pallidal
stimulation is neurologically safe compared
to the pallidotomy in which the incidence of
long term complications was noted in 10% in
a study comprising 138 patients.10

Our chronic results are close to those
reported when chronic stimulation was ap-
piled in the posteroventral part of the GPI,
in which reduction of the motor score of UPDRS
by 30–40% and an improvement of dyskinesia
by 60–70% was found.10 However, chronic
stimulation of the subthalamic nucleus could
give better results than stimulation of GPI
whatever the site of stimulation because a re-
cent retrospective study comparing stimula-
tion of subthalamic nucleus or GPi (postero-
ventral part) in young patients has shown a sig-
nificant higher improvement of the motor
score of the UPDRS, and a significant reduc-
tion of treatment when stimulation was
applied on subthalamic nucleus.16 However,
such a result needs to be confirmed by
randomised trials.

In summary, acute antemerial GPI
stimulation applied to the distal part of the
nucleus induces an improvement of parkinso-
nian signs when patients are in the off state
and of dyskinesia when they are in the on state.
Chronic results show that this is an effective
treatment for advanced Parkinson’s disease
with benefit sustained for at least 6 months,
which suggests that the procedure will be
effective for years. A survey of patients every 6
months is now in progress. However, this
surgical procedure needs to be evaluated with
a larger number of patients and to be compared
with other neurosurgical treatments such as
ventrolateral GPI and subthalamic stimulations.
9–10

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HISTORICAL NOTE

Some contributions of Duchenne de Boulogne (1806–75)

PROGRESSIVE MUSCULAR ATROPHY

In 1849 Duchenne described a patient with spreading progressive muscular atrophy that started in the hands and spread slowly to the arms and legs, with no sensory signs, pain, or sphincter disturbance. Characteristically self-efacing, he did not publish the case himself, but passed on his observations to François Amilcar Aran, physician to the Hôpital Saint Antoine. Aran published the case, and acknowledged: “I owe a thousand thanks to my friend Duchenne de Boulogne who freely put at my disposal all his material . . . .” Aran’s account (translated by G V Poree) followed in 1870: “Muscles . . . often jerked by little fibrillary or partial contractions . . . agitated with worm-like movements. Progressive muscular atrophy attacks the upper limbs, and destroys its muscles in an irregular fashion. It begins in such cases by attacking one after another the muscles of the thenar eminence, spreading from the superficial to the deep layer. As soon as the abductor pollicis is wasted, its absence is marked by a depression, and by the attitude, during repose, of the first metacarpal bone, which lies too close to the second . . . Depressions of the hypotrochlear eminence and interosseous next announce the atrophy of the muscles of those regions. The loss of the interossei muscles is shown by the claw-like attitude of the fingers . . . The atrophy may remain localised for some eight or nine years . . . Electromuscular contractility is normal—. . . beyond doubt.”

Pathologically, Duchenne reported the loss of striation, replacement by granular matter and fat vesicles, and fascicular atrophy of the muscles. But the atrophy is accompanied by a set-back by stating: “the feebleness of contractility . . . is chiefly the consequence of the wasting, . . . and not the result of paralysis, i.e. of a failure of the motor nerve action.”

MUSCLE DISEASE AND “DUCHENNE’S DYSTROPHY”

His investigations of muscle disease continued with his invention of the “harpoon” that he employed to perform percutaneous muscle biopsies; not surprisingly, this aroused hostile criticism of Duchenne’s ethical propriety in the local press. The discovery of pseudo-hypertrophic paralyis, or myo-sclerotic paralyis in 1868, was however, a remarkable and important contribution, dependent on and illustrated by pictures of histological obtained by harpoon biopsy: “This disease is mainly characterised: 1. By feebleness of movement, usually situated at first in the muscles of the lower extremities and of the lumbar spine, ultimately spreading progressively to the limbs; increasing in intensity till all movement is lost; 2. Increase in size of most of the parietic muscles; 3. Increase of the interstitial connective tissue of the parietic muscles, and in the more advanced stages by an abundant production of fibrous tissue or of fatty globules. The name I have given to this disease pseudo-hypertrophic muscular paralyis . . . has reference to the symptoms . . . It may be called myo-sclerotic paralyis, a name which is more scientific and justified by pathological anatomy.”

Of his many other contributions were original descriptions of the use of photography of microscopic structure, tibetic locomotor ataxia which contemporaries had confused with Friedreich’s disease, the anterior horn cell lesions, which caused acute poliomyelitis, and glossolabio-laryngeal paralyis (bulbar palsy).

Guillaume Benjamin Amand Duchenne was the son of a long lineage of seafarers and fishermen in the region of Boulogne sur Mer. According to Lasègue and Strauss, he was of middle height, thickset, active in movement, slow of speech and retaining to the last a faint provincial accent. He studied medicine in the University of Paris, under Laennec, Cruveilhier, and Dupuytren. He graduated in 1831. He returned to Boulogne to a limited private practice, but was badly affected by his young wife’s death in childbirth. He lived only for his patients and for his scholarship.

Lonely and isolated from his friends, he returned to Paris in 1842 and started to experiment with Faradic current on the function of skeletal muscle. He sought no formal appointments, but attended patients in many Parisian hospitals, questioning and examining patients with laborious obsession, often following their progress by visiting them in their homes for many years. At times, he was humiliated by established physicians: “the monarchs of the wards”, he called them. His reputation slowly increased, despite a neglect of pathological anatomy, and his dependence on his own observations for theoretical and neurological writings. Later in life he concentrated more on the nervous system than on muscles, taking up history with youthful zest. Both Charcot and Trousseau fostered his research work and showed him great respect: Charcot’s lectures contain frequent acknowledgement of his work.

Neither succinct as a writer, nor systematic in his work, his lengthy papers emerged slowly. His first, L’Electrisation Localisée et de son application à la pathologie et à la thérapeutique, was published in 1855, was well received, and encouraged more research and trials of electrotherapy, by 1872 it had added a third edition. In 1862 his previously estranged son joined him in Paris. He started, at last, to gain international respect. This culminated in election to many medical societies throughout Europe. A final disaster occurred when his son died of typhoid fever in 1871, with grave and lasting effects on his personal life. He died of a cerebral haemorrhage in 1875.

His epitaph we can leave to Charcot who remarked: “How is it that one fine morning Duchenne discovered a disease that probably existed in the time of Hippocrates? Why do we realise things so late, so poorly, with such difficulty . . . Because our minds have to take in something that upsets our original set of ideas . . .” A bas-relief in the Salpêtrière shows the doctor attending his patient, applying electrodes attached to a simple generator. The accompanying plaque reads:

A. Duchenne (de Boulogne)

Electrisation Localisée

Physiologie des Mouvements

Neuropathologie

Postscript: Edward Meryon (1807–) presented a paper to the Royal Medico-chirurgical society on 9 December, 1851, which described two typical “Duchenne” families and one with Becker type dystrophy. He recognised them as primary diseases of muscle and showed postmortem the typical “granular degeneration”

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Acute and chronic effects of anteromedial globus pallidus stimulation in Parkinson's disease
Franck Durif, Jean-Jacques Lemaire, Bérengère Debilly and Gérard Dordain

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